The Association of Mediterranean Diet during Pregnancy with Longitudinal Body Mass Index Trajectories and Cardiometabolic Risk in Early Childhood

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Objective To evaluate the associations between maternal adherence to the Mediterranean diet during pregnancy and their offspring's longitudinal body mass index (BMI) trajectories and cardiometabolic risk in early childhood.

Study design We included mother-child pairs from the Infancia y Medio Ambiente (INMA) longitudinal cohort study in Spain. We measured dietary intake during pregnancy using a validated food frequency questionnaire and calculated the relative Mediterranean diet score (rMED). We estimated offspring's BMI z score trajectories from birth to age 4 years using latent class growth analyses (n = 2195 mother-child pairs). We measured blood pressure, waist circumference, and cardiometabolic biomarkers to construct a cardiometabolic risk score at 4 years (n = 697 mother-child pairs). We used multivariable adjusted linear and multinomial regression models.

Results A higher maternal rMED in pregnancy was associated with a lower risk in offspring of larger birth size, followed by accelerated BMI gain (reference trajectory group: children with average birth size and subsequent slower BMI gain) (relative risk of high vs low rMED score, 0.68; 95% CI, 0.47-0.99). rMED score during pregnancy was not associated with the cardiometabolic risk score, its components, or related biomarkers.

Conclusions Higher adherence to the Mediterranean diet in pregnancy was associated with lower risk of having offspring with an accelerated growth pattern. This dietary pattern was not associated with the offspring's cardiometabolic risk at 4 years. *(J Pediatr 2018;■■:■■-■■).*

The Mediterranean diet is a healthy dietary pattern characterized by a high content of fruits, vegetables, olive oil, legumes, and nuts. This dietary pattern has been associated with a lower risk of central obesity and cardiometabolic risk in adults.[1] Related data in children are scarce, however.[2] An intervention study found that children who consumed a Mediterranean diet over a 4-month period presented on average with decreases in body mass index (BMI), fat mass, and serum levels of triglycerides (TG) and high-density lipoprotein (HDL) cholesterol.[3]

There is some evidence indicating that early life factors (those occurring in utero or during the first 2 years of life) also may influence the future obesity and cardiometabolic risk.[4] In our previous analyses using data from the Infancia y Medio Ambiente (INMA) birth cohorts, we observed that adherence to a Mediterranean

apo	Apolipoprotein	INMA	Infancia y Medio Ambiente
BMI	Body mass index	rMED	Relative Mediterranean Diet Score
BP	Blood pressure	RR	Relative risk
CRP	C-reactive protein	SBP	Systolic blood pressure
DBP	Diastolic blood pressure	TG	Triglycerides
FFQ	Food-frequency questionnaire	WC	Waist circumference
HDL	High-density lipoprotein		
IDEFICS	Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants		

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diet during pregnancy was associated with smaller waist circumference (WC) at age 4 years,[5] although we found no clear association with BMI at age 4 years. BMI at 4 years represents a measure of general adiposity at one time point; it has been argued that growth trajectories may be more relevant for assessing adiposity risk in children.[6] Specific growth trajectories, especially these involving accelerated growth, have been related to increased risk of obesity and cardiovascular disease later in life.[7-10] Studies have found a prenatal influence of maternal Mediterranean diet on child cardiometabolic biomarkers (eg, low-density lipoprotein, apolipoprotein (apo) B, and insulin concentrations) at birth, but not HDL, TG, and leptin.[11-13] Another study conducted in the US and Greece of the association between a maternal Mediterranean diet in pregnancy and cardiometabolic outcomes in mid-childhood found an inverse association between Mediterranean diet and blood pressure (BP) and leptin values.[14]

The aim of the present study was to evaluate the association between maternal adherence to the Mediterranean diet during pregnancy and offspring's longitudinal BMI trajectories and cardiometabolic risk in early childhood.

Methods

We recruited pregnant women between 2003 and 2008 in the 4 Spanish regions of Asturias, Gipuzkoa, Sabadell, and Valencia as part of the population-based INMA birth cohort study.[15] Inclusion criteria were pregnant women age ≥16 years, intention to deliver at the reference hospital, ability to communicate in Spanish or regional languages, singleton pregnancy, and no assisted conception. We recruited 2762 pregnant women at prenatal visits during the first trimester of pregnancy at public health care centers or hospitals. The women were then followed up during the third trimester, and their offspring were evaluated at age 6 months, 1 year, and 4 years. The flowchart of study participation is shown in **Figure 1** (available at www.jpeds.com). Our study cohort included 2195 pairs of mothers and children for the study of growth trajectories and 697 pairs of mothers and children for the study of cardiometabolic risk. The study was approved by hospital and institutional Ethics Committees in each region, and all participants provided written informed consent.

We assessed maternal diet in the first trimester (week 12) and third trimester (week 32) of pregnancy using a 101-item food-frequency questionnaire (FFQ). This FFQ was developed and validated for use among pregnant women living in Spain, with satisfactory coefficients for validity and reproducibility.[16] At week 12 of pregnancy (first trimester), we asked the mothers about their diet during the first trimester of pregnancy, and at week 32 (third trimester), we asked about their diet between weeks 12 and 32 of pregnancy. The FFQ specified standard units and serving sizes for each food item. Nutrient values and total energy intake calculated based on the US Department of Agriculture's food composition tables and other published national sources.[17,18]

We assessed adherence to the Mediterranean diet using the relative Mediterranean Diet Score (rMED).[19] The rMED was constructed with the data obtained from the FFQ during the first and third trimesters. The rMED was constructed taking into account the consumption of vegetables, fruits and nuts, cereals, legumes, fish, olive oil, meat, and dairy products. To adapt the score to pregnant women, the component on alcohol consumption was removed because the recommendation is to avoid alcohol consumption during pregnancy and most of the women in our cohort did not consume it. All the food groups were measured as grams per 1000 kcal/day, and values were divided into tertiles. We assigned values of 0, 1, and 2 to the intake tertiles, positively scoring higher intakes for the 6 components that fit into the Mediterranean diet. The scoring was reversed for meat and dairy components presumed to not fit into the Mediterranean diet, thus positively scoring lower intakes.

Scores were summed for each component, for a total score ranging from 0 to 16. The score was further divided into tertiles to identify those with low (tertile 1), medium (tertile 2), and high (tertile 3) adherence to the Mediterranean diet.

Weight and height at different age points (from birth to 4 years) were extracted from medical records. BMI (weight in kilograms/length in square meters) was used to estimate age- and sex-specific *z* scores based on World Health Organization reference values.[20] Trained staff measured WC at age 4 years to the nearest 0.1 cm using an inelastic tape (model 201; SECA, Hamburg, Germany) at the midpoint between the lowest rib margin and the iliac crest in a standing position and after gentle expiration, using standard protocols. We then calculated age-, sex-, and region-specific WC *z* scores. WC was not available for the Gipuzkoa region, and thus this region was excluded from analyses using WC.

We used repeated weight and height measures from birth to age 4 years extracted from medical records (a mean of 11 ± 3.4 measures per child). We calculated age- and sex-specific BMI *z* scores using the World Health Organization growth standards and[20] estimated longitudinal BMI z score trajectories from birth to age 4 years using latent class growth analysis,[6,21] which allows parameter differences to be captured across unobserved subpopulations by assuming a number of discrete latent classes. The difference between this model and the common linear mixed models is that the fixed effects and the random distribution effect can be specific of each class. We tested between 2 and 7 possible trajectory classes, and based on the Akaike and Bayes information criteria, we chose the model with 5 BMI trajectories because it had the best data fit and the lowest estimated Akaike and Bayes information criteria, which measure goodness of fit. We also considered the distribution of the cases over the different trajectories and found that the possible trajectories were meaningful. The 5 BMI trajectories are distinct according to size at birth (BMI *z* score at birth defined for comparison purposes as lower, average, or higher), and the BMI z score trajectories after birth are defined for comparison purposes as slower or accelerated (**Figure 2**; available at www.jpeds.com).[22] Based on these features, the 5 trajectories are: class 1, larger birth size with subsequent accelerated BMI gain; class 2, larger birth size with subsequent slower BMI gain; class 3, smaller birth size with subsequent accelerated BMI gain;

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class 4, average birth size with subsequent slower BMI gain; and class 5, smaller birth size with subsequent slower BMI gain. Class 4, average birth size and slower BMI gain, was considered the reference group in our statistical analysis.

Study-trained personnel measured systolic BP (SBP) and diastolic BP (DBP) at 4 years once after 5 minutes of rest at the primary health center, using a digital automatic monitor (CPII; OMRON Health Care, Bannockburn, Illinois) and a special cuff adjusted to the child's upper right arm size. We calculated the average BP as the average between SBP and DBP. We used SBP, DBP, and average BP values to calculate the age-, sex-, height-, and region-specific *z* scores using our population means.[23,24] The measures were standardized for the INMA regions (Sabadell, Valencia, and Asturias; BP was not measured in Gipuzkoa) to account for the regional differences in the INMA Project.[24]

Lipid concentrations were measured in nonfasting blood samples collected at age 4 years. HDL, TG, apo A1, and apo B were assayed using standard analytical techniques (ABX-Pentra 400; Horiba Medical, Kyoto, Japan).[25] We used the HDL, TG, apo A1, and apo B values to calculate age-, sex-, and region-specific *z* scores.

Offspring's metabolic risk at age 4 years was determined by means of a continuous cardiometabolic risk score, based on the Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects In Children and Infants (IDEFICS) study definition.[23] We used the sums of the age-, sex-, and region-specific *z* scores for the individual risk score components: WC, BP, and lipids. We used the mean of TG and of the inverse of HDL as an indicator of lipid concentrations:

$$\text{CM-risk score} = (\text{WC z score}) + (\text{BP z score}) + \left[\frac{(\text{-HDL-C z score} + \text{TGs z score})}{2}\right]$$

We did not have information on glucose or insulin concentrations and so could not include these variables in our score. We calculated the cardiometabolic risk score only in the population with available data on WC, BP, TG, and HDL at 4 years (n = 697). Data from the Gipuzkoa region was not included because WC and BP data were not available for this region. A higher cardiometabolic score indicated a higher cardiometabolic risk at age 4 years.[26]

In the nonfasting blood samples collected at 4 years, we measured plasma leptin, c-peptide, interleukin (IL)-6, adiponectin, and C-reactive protein concentrations using either standard analytical techniques (ABX-Pentra 400; Horiba Medical, Kyoto, Japan), enzyme-linked immunosorbent assay (Genway Biotek, San Diego, California) or Luminex assays (Luminex Corp; Madison, Wisconsin), as described in **Table I** and **Table II** (available at www.jpeds.com). We calculated sex-, age-, and region-specific *z* scores for all these biomarkers.

Descriptive statistics compared sociodemographic characteristics of mother and children included in our study by level of maternal adherence to the Mediterranean diet during pregnancy. Statistical significance in the observed differences was assessed using the χ^2 test for categorical variables and ANOVA for continuous variables. We used the maternal rMED (in 2-point increases and in tertiles) in the third trimester of pregnancy as the exposure variable, because we considered a priori this trimester more relevant for offspring growth.[27]

We used multinomial logistic regression models to assess the association between maternal rMED (in tertiles) and child early-life BMI trajectories from birth to age 4 years. Effect estimates from the models were then exponentiated to calculate relative risk (RR) ratios.

We used linear regression models to estimate the β coefficients for the association between rMED (expressed in tertiles) and the continuous cardiometabolic risk score, its components, and cardiometabolic biomarkers at age 4 years. Based on previous knowledge, we considered the following variables as important confounders: cohort, maternal social class and educational level, maternal prepregnancy BMI (based on measured height at recruitment and prepregnancy self-reported weight), weight gain during pregnancy (extracted from prenatal visit records), maternal physical activity during pregnancy (total and leisure time physical activity in pregnancy in metabolic equivalents-hour/day), gestational diabetes, smoking during pregnancy, parity, maternal age at delivery, predominant breastfeeding duration (weeks), child sex, child BMI *z* score at age 4, and child age at biomarkers and anthropometry measurements.

The selected covariates included in the final models were those that influenced the association between the exposure and outcome of interest using backward stepwise selection method ($P < .20$).

Multinomial and linear regression models were adjusted using 2 sets of confounders. Model 1 was a minimally adjusted model including child age, sex, and region. Model 2 included age, sex, and those covariates found to influence the rMED-outcome association of interest in analysis for confounder selection. The set of confounders included in model 2 was specific to each outcome. We used the multivariate nutrient density method and then adjusted model 2 for total energy intake during pregnancy to control the potential measurement error.[28]

For all the models, we calculated the *P* value for trend using the exposure variable in tertiles as continuous. In main analysis, we used the maternal rMED (in tertiles) in the third trimester of pregnancy as the main exposure variable because we considered a priori this trimester biologically more relevant for offspring postnatal growth.[27] However, as a sensitivity analysis, we repeated all analyses using rMED in the first trimester to test whether the diet in this trimester also had associations with postnatal growth and cardiometabolic risk in childhood. We also performed the analyses involving growth trajectories with only the participants attending the 4-year visit (n = 1837) and the population with available data for the cardiometabolic risk score (n = 697). We estimated implausible energy reporting based on the ratio of reported energy intake to predicted energy requirements as described by Huang et al.[29,30] We ran the analyses adjusting for this implausible energy reporting.

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Models were stratified by child sex to test whether the effects were homogeneous between these subgroups. We tested for interaction between exposure and child sex. To assess heterogeneity among regions in the studied associations, we calculated region-specific estimates using general linear models and polynomial models, and we used random-effects meta-analyses (I^2) to pool the estimates.

We repeated all analyses as complementary analyses, further adjusting for child diet (rMED) at 4 years. However, the effect estimates did not change substantially, and thus these data are not presented here. To account for missing data in confounders, we performed multiple imputation using chained equations, we generated and analyzed 20 completed datasets using the standard combination rules for multiple imputations.[31]

All statistical analyses were performed using the Stata 12.1 (StataCorp, College Station, Texas).

Results

Table III presents characteristics of mothers and children from the INMA project (n = 2195), according to tertiles of adherence to Mediterranean diet using the rMED score. Mothers with lower adherence to Mediterranean diet were younger, had greater energy intake, were more likely to be smokers, and had lower social and educational levels compared with women with greater adherence to the Mediterranean diet. There were some differences across the 4 INMA regions; adherence was higher in Asturias and Gipuzkoa and lower in Sabadell and Valencia. Offspring of mothers with lower adherence to the Mediterranean diet received predominant breastfeeding for a shorter time compared with offspring of mothers with greater adherence to the Mediterranean diet during pregnancy.

We compared characteristics between mothers included in the study (n = 2195) and those lost to follow-up (n = 567). Those lost to follow-up were younger, smoked more, and had lower socioeconomic and education levels. We also compared the characteristics of mothers and children included in the growth trajectories analyses (n = 2195) and included in the cardiometabolic analyses (n = 697) and found no differences.

Children with class 1 and 2 trajectories included children of mothers who had greater gestational weight gain (P <.001), and these mothers were more likely to be multiparous (P <.001) compared with mothers of children of small or average birth

Table III. Characteristics of mothers and children by maternal adherence to the Mediterranean diet at the third trimester of pregnancy (in tertiles of rMED score) (n = 2195)

Characteristics	n	T1 (n = 925; 42.1%)	T2 (n = 631; 28.8%)	T3 (n = 639; 29.1%)	*P*
Maternal characteristics					
Age at delivery, y, mean (SD)	2195	30.2 (4.4)	31.1 (4.0)	31.4 (3.9)	<.001
Smoking in pregnancy, %					
No	1807	77.4	83.8	88.9	<.001
Yes	381	22.6	16.2	11.1	
Social class, %					
I + II	495	18.6	23.2	27.7	<.001
III	586	24.2	29.2	27.9	
IV + V	1113	57.2	47.6	44.4	
Education level, %					
Primary or less	112	28.0	20.7	17.5	<.001
Secondary	913	42.5	43.1	39.0	
University	778	29.4	36.2	43.5	
Physical activity, METS (h/d), mean (SD)	2195	37.2 (3.1)	37.4 (3.0)	37.6 (3.2)	.061
Prepregnancy BMI, kg/m^2, mean (SD)	2195	23.5 (4.1)	23.6 (4.1)	23.5 (4.3)	.834
Pregnancy EI, kcal, mean (SD)	2195	2178.5 (504.5)	2058.3 (448.9)	1949.6 (393.0)	<.001
Pregnancy weight gain, kg/wk, mean (SD)	2127	0.35 (0.13)	0.35 (0.12)	0.34 (0.13)	.017
Diabetes, %					
None	2067	95.9	96.0	94.9	.590
Gestational diabetes	88	3.8	3.5	4.9	
Diabetes in previous pregnancy	7	0.3	0.5	0.2	
Parity, %					
Primiparous	1249	54.0	57.2	61.0	.062
Multiparous	944	46.0	42.8	39.0	
Child characteristics					
Sex, %					
Female	1059	47.2	48.8	49.1	.720
Male	1136	52.8	51.2	50.9	
Age at measurements, y, mean (SD)	1841	4.39 (0.19)	4.42 (0.17)	4.43 (0.18)	<.001
INMA region, %					
Asturias	404	15.0	19.7	22.1	<.001
Gipuzkoa	537	17.1	24.4	35.2	
Sabadell	558	27.5	27.1	20.8	
Valencia	696	40.4	28.8	21.9	
Birth weight, g, mean (SD)	2158	3324.8 (409.0)	3370.2 (375.5)	3343.1 (402.6)	.092
Predominant breastfeeding, wk, mean (SD)	2158	11.8 (9.6)	12.3 (9.6)	13.1 (9.6)	.049
BMI *z* score, mean (SD)	1837	0.6 (1.1)	0.6 (1.1)	0.6 (1.0)	.646

EI, energy intake; *METS*, metabolic equivalents.
The rMED score ranges from 0 to 15, in 3 tertiles, to define low (T1, range 0-7), medium (T2, range 8-9), and high (T3, range 10-15) adherence to the Mediterranean diet.

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size. Children with class 1 and 3 trajectories had mothers with higher prepregnancy BMI, and they had higher BMI and WC *z* scores at 4 years compared with children with slow growth (**Table IV**; available at www.jpeds.com).

Table V shows the association between maternal rMED score in the third trimester of pregnancy and offspring BMI trajectories from birth to age 4 years.

A higher rMED score was associated with lower RR for the child to have a BMI *z* score trajectory departing from larger birth size and showing a subsequent accelerated BMI gain (RR of high vs low rMED, 0.64; 95% CI, 0.45-0.92, with a significant trend across tertiles; $P = .022$) compared with children in the reference trajectory (class 4: average birth size, slower growth). This association remained after controlling for potential confounders, such as maternal prepregnancy BMI and gestational weight gain (RR of high vs low rMED, 0.68; 95% CI, 0.47-0.99; *P* for trend across tertiles = .059) and potential mediators, such as gestational age.

We found no association between rMED score during pregnancy and other BMI trajectories. We also did not observe an association between maternal Mediterranean diet and child cardiometabolic risk score in any of the models studied, although this analysis included fewer observations (**Table VI**). There were null associations between maternal rMED score and the components of the cardiometabolic risk factors (DBP, SBP, HDL, and TG z scores) in the 2 models studied, except for a previously reported inverse association with WC (β, −0.10; 95% CI, −0.18 to −0.02; *P* for trend = .013).[5] **Table VI** also shows the association between maternal rMED score in the third trimester of pregnancy and other related biomarkers in a subsample of the INMA cohort with available data. Although there was a modest tendency toward a lower leptin *z* score (model 2: β, −0.16; 95% CI, −0.36 to 0.04), lower adiponectin (model 2: β, −0.32; 95% CI, −0.98 to 0.34), and higher apo A1 (model 2: β, 0.20; 95% CI, −0.03 to 0.42) in offspring of mothers with higher rMED score, these associations were not statistically significant. There were null associations between rMED score and child c-peptide, apo B, IL-6, and CRP.

In sensitivity analyses, rMED score at the first trimester was not associated with any of the longitudinal growth patterns (**Table VII**; available at www.jpeds.com), and the estimates of the association with cardiometabolic risk score and the biomarkers were similar to those with rMED score at the third trimester. rMED score at the first trimester was associated with higher apo A1 concentrations (high vs low rMED score: β, 0.28; 95% CI, 0.07-0.49) (**Table VIII**; available at www.jpeds.com).

The estimates of the association between rMED score at the third trimester and longitudinal growth patterns were similar when limiting the analyses to participants with anthropometric data at age 4 years and to participants with cardiometabolic risk data (n = 697) (data not shown).

In stratified analyses, the association between rMED score at the third trimester and the class 1 longitudinal growth trajectories was stronger in boys compared with girls (rMED T3 vs T1: RR, 0.43; 95% CI, 0.24- 0.77 vs 0.95; 95% CI, 0.58-1.57), but the *P* value for interaction was not significant (*P* for

Table V. Associations of maternal adherence to the Mediterranean diet at the third trimester of pregnancy and offspring growth trajectories from birth to age 4 years in the INMA project (n = 2195)

rMED Range	Model 1				*P* for trend	Model 2				*P* for trend
	2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9), RR (95% CI)	High: T3 (10-15), RR (95% CI)		2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9), RR (95% CI)	High: T3 (10-15), RR (95% CI)	
Class 1 (n = 263): larger birth size, accelerated growth	0.90 (0.81-1.01)	Ref	0.98 (0.71-1.37)	0.64 (0.45-0.92)	.022	0.92 (0.81-1.03)	Ref	1.02 (0.73-1.43)	0.68 (0.47-0.99)	.059
Class 2 (n = 574): larger birth size, slower growth	1.02 (0.93-1.11)	Ref	1.01 (0.77-1.31)	0.93 (0.71-1.21)	.607	1.04 (0.95-1.13)	Ref	1.04 (0.79-1.36)	0.98 (0.74-1.28)	.891
Class 3 (n = 293): smaller birth size, accelerated growth	0.99 (0.89-1.10)	Ref	1.03 (0.74-1.43)	0.96 (0.69-1.34)	.837	0.96 (0.86-1.08)	Ref	1.00 (0.71-1.40)	0.91 (0.64-1.28)	.603
Class 5 (n = 274): smaller birth size, slower growth	0.95 (0.85-1.06)	Ref	0.87 (0.62-1.22)	0.84 (0.60-1.19)	.299	0.93 (0.83-1.04)	Ref	0.79 (0.58-1.17)	0.79 (0.55-1.12)	.165

rMED score ranged from 0 to 15, in 3 tertiles to define low (T1), medium (T2), and high (T3) adherence to the Mediterranean diet. The reference group for the outcome is class 4 (average birth size, slower growth trajectory; n = 791).
Model 1: Multinomial logistic regressions adjusted for child sex, age, and INMA region.
Model 2: Model 1 further adjusted for maternal age, maternal prepregnancy BMI, smoking during pregnancy, maternal total EI, gestational weight gain, physical activity (third trimester), and parity.

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Table VI. Associations of maternal adherence to the Mediterranean diet at the third trimester of pregnancy and offspring cardiometabolic risk score, components of the score, and related biomarkers at age 4 years

	Model 1					Model 2				
rMED Range	2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9) β (95% CI)	High: T3 (10-15) β (95% CI)	*P* for trend	2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9) β (95% CI)	High: T3 (10-15) β (95% CI)	*P* for trend
Metabolic risk score* (n = 697)	0.02 (–0.07 to 0.11)	Ref	0.08 (–0.20 to 0.35)	–0.06 (–0.34 to 0.23)	.780	0.00 (–0.09 to 0.09)	Ref	0.06 (–0.21 to 0.34)	–0.11 (–0.40 to 0.18)	.528
WC *z* score* (n = 1418)	–0.01 (–0.06 to 0.03)	Ref	0.00 (–0.13 to 0.12)	–0.07 (–0.20 to 0.06)	.339	–0.03 (–0.05 to 0.00)	Ref	–0.03 (–0.10 to 0.04)	–0.10 (–0.18 to –0.02)	.013
SBP *z* score† (n = 1362)	0.03 (–0.01 to 0.07)	Ref	0.02 (–0.11 to 0.14)	0.09 (–0.05 to 0.22)	.238	0.04 (–0.01 to 0.08)	Ref	0.03 (–0.10 to 0.16)	0.11 (–0.03 to 0.24)	.143
DBP *z* score† (n = 1362)	0.00 (–0.04 to 0.04)	Ref	0.04 (–0.08 to 0.17)	0.04 (–0.10 to 0.17)	.534	0.01 (–0.03 to 0.05)	Ref	0.06 (–0.07 to 0.18)	0.05 (–0.08 to 0.19)	.395
HDL *z* score‡ (n = 939)	0.01 (–0.04 to 0.06)	Ref	0.00 (–0.15 to 0.16)	0.04 (–0.12 to 0.20)	.602	0.01 (–0.04 to 0.07)	Ref	0.01 (–0.14 to 0.17)	0.06 (–0.10 to 0.23)	.449
TG *z* score‡ (n = 940)	0.00 (–0.05 to 0.05)	Ref	–0.01 (–0.16 to 0.15)	–0.01 (–0.16 to 0.15)	.944	–0.01 (–0.06 to 0.04)	Ref	–0.03 (–0.18 to 0.13)	–0.03 (–0.19 to 0.14)	.728
Leptin *z*-acore§ (n = 459)	–0.02 (–0.10 to 0.05)	Ref	0.00 (–0.22 to 0.23)	–0.17 (–0.40 to 0.06)	.166	–0.04 (–0.10 to 0.03)	Ref	–0.05 (–0.24 to 0.14)	–0.16 (–0.36 to 0.04)	.125
C-peptide *z* score§ (n = 459)	–0.02 (–0.10 to 0.06)	Ref	0.08 (–0.15 to 0.30)	–0.11 (–0.34 to 0.12)	.383	–0.04 (–0.12 to 0.04)	Ref	0.04 (–0.18 to 0.27)	–0.14 (–0.38 to 0.09)	.252
Adiponectin *z* score§ (n = 75)	–0.09 (–0.28 to 0.09)	Ref	–0.06 (–0.63 to 0.52)	–0.32 (–0.90 to 0.27)	.299	–0.10 (–0.31 to 0.10)	Ref	–0.09 (–0.72 to 0.54)	–0.32 (–0.98 to 0.34)	.347
Apo A1 *z* score¶ (n = 522)	0.07 (0.00 to 0.14)	Ref	0.08 (–0.13 to 0.29)	0.16 (–0.06 to 0.38)	.143	0.08 (0.01 to 0.15)	Ref	0.11 (–0.10 to 0.32)	0.20 (–0.03 to 0.42)	.082
Apo B z score¶ (n = 522)	0.05 (–0.02 to 0.12)	Ref	0.09 (–0.12 to 0.30)	0.15 (–0.06 to 0.37)	.161	0.04 (–0.03 to 0.11)	Ref	0.08 (–0.14 to 0.29)	0.11 (–0.11 to 0.34)	.318
IL-6 *z* score** (n = 242)	0.09 (–0.01 to 0.20)	Ref	0.05 (–0.28 to 0.39)	0.15 (–0.18 to 0.47)	.358	0.09 (–0.02 to 0.20)	Ref	0.10 (–0.24 to 0.45)	0.17 (–0.16 to 0.50)	.315
CRP *z* score** (n = 685)	–0.02 (–0.08 to 0.04)	Ref	–0.05 (–0.22 to 0.13)	–0.06 (–0.24 to 0.13)	.542	–0.02 (–0.08 to 0.04)	Ref	–0.04 (–0.22 to 0.14)	–0.05 (–0.24 to 0.14)	.599

rMED score ranges from 0 to 15, in 3 tertiles representing low (T1), medium (T2), and high (T3) adherence to the Mediterranean diet. Metabolic risk score: sex-, age-, and region-specific HDL *z* score, TG *z* score, average between height, age-, sex-, and region-specific SBP and DBP *z* scores and sex-, age-, and region-specific WC *z* score. Based on IDEFICS score.

Model 1: General linear regressions adjusted for child sex, age, and region.

*Model 2: General linear regressions adjusted for child sex, age, region, maternal educational level, maternal total EI, parity, and child BMI *z* score at 4 years.

†Model 2: General linear regressions adjusted for child sex, age, region, maternal educational level, maternal total EI, maternal prepregnancy BMI, gestational weight gain, and maternal physical activity.

‡Model 2: General linear regressions adjusted for child sex, age, region, maternal social class, maternal total EI, maternal prepregnancy BMI, gestational weight gain, and maternal physical activity.

§Model 2: General linear regressions adjusted for child sex, age, region, maternal educational level, maternal smoking, maternal total EI, maternal prepregnancy BMI, gestational weight gain, parity, and child BMI *z* score at 4 years.

¶Model 2: General linear regressions adjusted for child sex, age, region, maternal age, maternal smoking, maternal prepregnancy BMI, gestational diabetes, maternal total EI, and parity.

**Model 2: General linear regressions adjusted for child sex, age, region, maternal age, maternal educational level, maternal smoking, maternal total EI, and maternal physical activity.

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interaction = 0.748). We did not find any effect modification in the associations between rMED score and the biomarkers studied after stratification by child sex. In the analyses adjusting for implausible energy reporting (14.78% of sample), the estimates were similar to the main analyses (data not shown).

In the meta-analyses, all results were homogeneous across the regions (data not shown).

Discussion

Our analyses detected 5 child longitudinal BMI trajectories from birth to age 4 years in the INMA project cohort. These growth patterns are consistent with previous BMI trajectories described in other populations.[7,9,32,33] Some longitudinal BMI trajectories have been associated with an increased risk of later obesity, mainly those that included accelerated growth.[9] The "accelerated postnatal growth hypothesis" links rapid weight gain in infancy and early childhood with increased risk of later obesity and other chronic diseases.[34] Notably, this association has been shown to be independent of birth weight, as both smaller and larger birth size are associated with accelerated postnatal growth. Several studies conducted in different populations have identified this "accelerating" growth pattern, and this pattern has been associated with an increased risk of overweight and higher blood pressure later in life.[7-10]

In a previous study in the same INMA cohort, we found that the Mediterranean diet was not associated with child BMI at age 4 years.[5] In contrast, in the present study, we used several measures of BMI at different time points, taking into account the dynamics of BMI over time. We found that offspring's larger birth size and accelerated growth were associated with maternal adherence to the Mediterranean diet during late pregnancy, but not with the maternal dietary pattern during the first trimester. It is biologically plausible that fetal nutrition supply could vary from early to late pregnancy. The second and third trimesters of pregnancy could be more critical periods for offspring's susceptibility to obesity, because this is when adipogenesis and fat accumulation mostly occur.[35,36]

These findings support the hypothesis that a healthy diet during pregnancy may have a protective role for the child to prevent an adverse BMI trajectory in early childhood. The potential mechanism behind this association could involve epigenetic modifications that regulate fetal cardiometabolic programming, as well as the shared environment within the family; the potential mechanism should be disentangled with further studies.

In these analyses, we did not find an association between maternal adherence to the Mediterranean diet during pregnancy and cardiometabolic risk in childhood, except for a positive association with apo A1 when we used dietary data collected during the first trimester of pregnancy. A similar study conducted using pooled data from 2 birth cohorts from Greece (RHEA cohort) and the US (Project Viva) found an associated between better adherence to the Mediterranean diet in pregnancy and lower SBP, DBP, and leptin levels and higher HDL levels in offspring during childhood.[14] The differences between that study and our present results might be explained by the different sample size (the INMA sample size for biomarker analyses was smaller), as well as by the different ages of participants in Project Viva (mean 7.7 years). There may be other differences related to adherence to the Mediterranean diet in these settings, which may lead to different associations. In addition, the scoring system used to calculate adherence to the Mediterranean diet also differed.

Other studies have explored the influence of dietary intake during pregnancy and offspring blood pressure and lipid biomarkers, most of which found null or inconsistent associations.[37-41] For example, 2 studies in a Danish cohort found no associations between glycemic index and protein intake during pregnancy and offspring blood pressure, HDL, or TG at age 20 years and but positive associations between the glycemic index and the homeostatic model assessment of insulin resistance score and leptin and total cholesterol levels.[37,38] In the Avon Longitudinal Study of Parents and Children (ALSPAC), maternal intake of several macronutrients and micronutrients was not associated with blood pressure at age 7.5 and 15 years.[39] In the Generation R cohort, maternal dietary intake was not associated with offspring blood pressure at age 6 years.[40] In contrast, in an Australian study, protein:carbohydrate, polyunsaturated fatty acids intake, and n-6 fatty acids in pregnancy were associated with higher SBP in offspring at age 4 years.[41]

There may be several explanations for the null results with the cardiometabolic risk score and related biomarkers. First, the effects of prenatal exposures on cardiometabolic risk might not appear until later in childhood, as has been observed in previous studies exploring the influences of large for gestational age status and early BMI trajectories on the development of cardiometabolic risk. We found a statistically significant association between maternal adherence to the Mediterranean diet assessed at the first trimester of pregnancy and child serum apo A1 concentrations. Although this result should be interpreted with caution owing to the multiple comparisons conducted in sensitivity analyses, it might be possible that the first trimester of pregnancy is more important for programming the lipid profile, as reported in a Dutch study showing altered lipid profiles in offspring of mothers exposed to famine in early gestation but not in offspring of mothers exposed to famine in late gestation.[42,43] In contrast, offspring of women exposed to famine in late gestation had glucose abnormalities, suggesting that the effects of maternal nutrition effect on offspring's development may depend on gestational timing.[44]

Limitations of this study include the use of nonfasting blood samples due to the young age of children (4 years). We used different biochemical techniques to measure some of the biomarkers in some regions; to minimize these differences, we used region-specific *z* scores for each biomarker and also adjusted all the models for region and performed a meta-analysis to test for heterogeneity among regions. Another limitation involves the measurement of BP in children, which is subject to measurement error. Owing to the lack of consensus criteria for metabolic syndrome in childhood, we constructed a cardiometabolic risk score based on the IDEFICS definition[23]; however, we could not include glycemia as a

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component, because glucose was not measured. Sample size varied for the different outcomes assessed, because data availability differed across regions. We were able to adjust our statistical models for major confounders, but the possibility of residual confounding always exists in observational studies. Regarding the reported significant associations among maternal rMED score, growth trajectories, and biomarkers, we cannot rule out the possibility that these are chance findings owing to the multiple comparisons performed. Finally, the use of a self-reported FFQ may be subject to misreporting and measurement error.

In conclusion, our findings suggest that greater adherence to the Mediterranean diet in the third trimester of pregnancy is associated with lower risk of having offspring with larger birth size and accelerated growth, but not with cardiometabolic risk in childhood. Given that longitudinal growth patterns that involve accelerated growth may be detrimental for the development of chronic metabolic diseases, detecting potential early-life determinants of longitudinal BMI trajectories is of special interest. ■

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A full roster of the INMA Project Investigators can be found at http://www.proyectoinma.org/presentacion-inma/listado-investigadores/en_listado-investigadores.html

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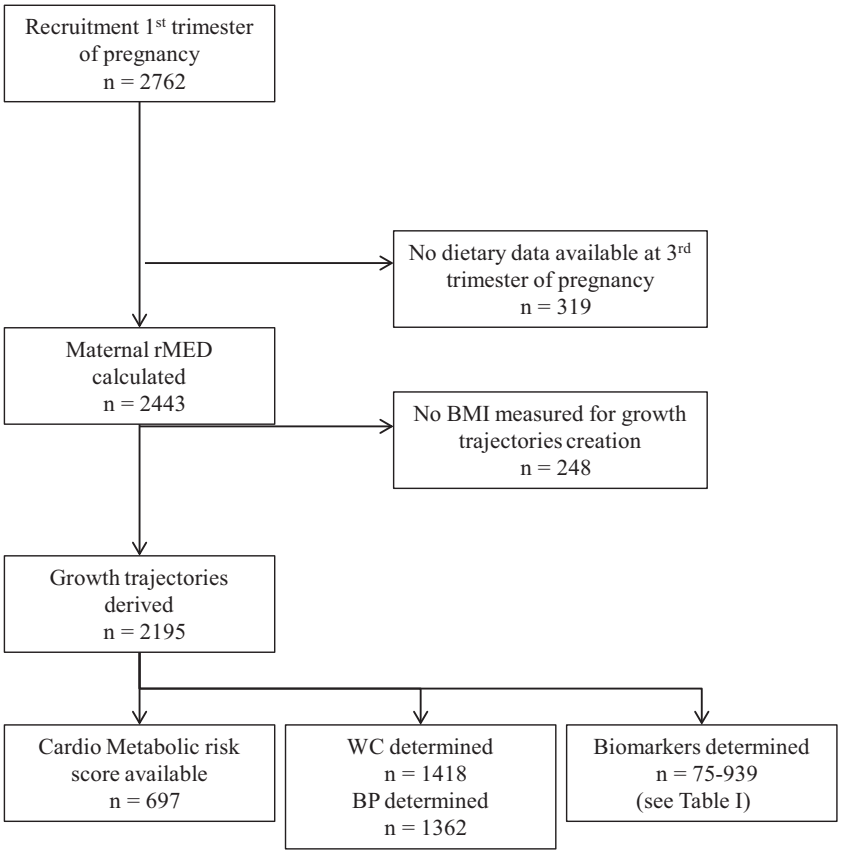

Figure 1. Flow chart describing the selection process of INMA project participants for the present analyses.

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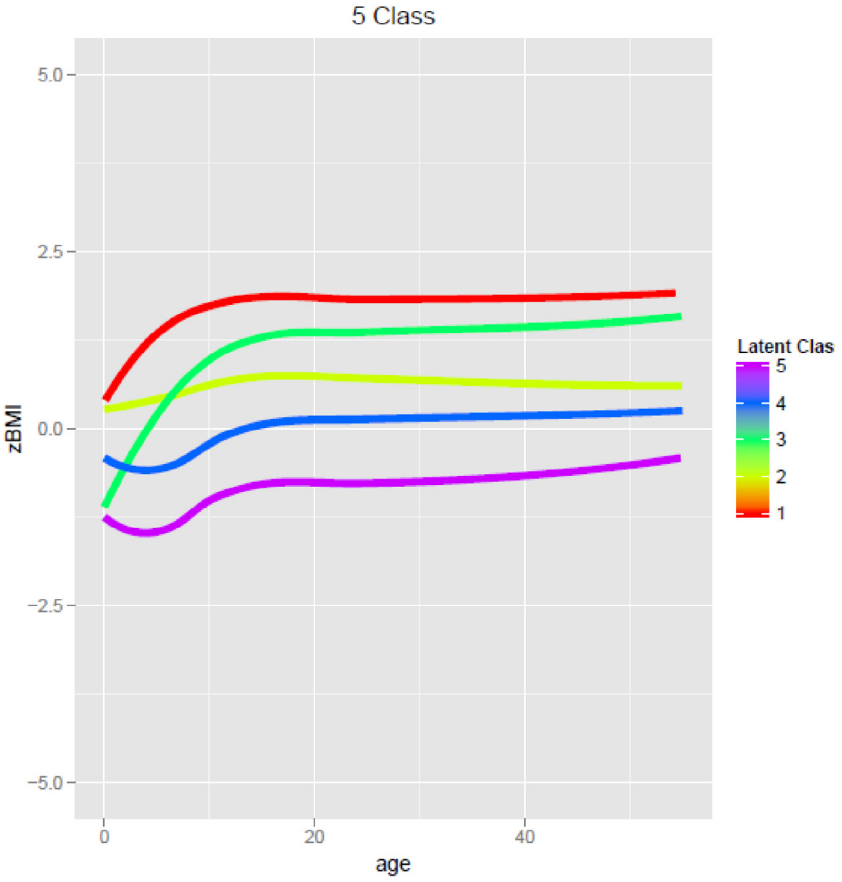

Child body mass index z-score longitudinal growth trajectories class from birth to 4 years of age in the INMA project.

Growth Trajectory	Frequency (n, %)	Description	
		Birth size (BMI)	BMI gain
Class 1	n = 263, 12.0%	Higher	Accelerated
Class 2	n = 574, 26.2%	Higher	Slower
Class 3	n = 293, 13.4%	Lower	Accelerated
Class 4	n = 791, 36.0%	Average	Slower
Class 5	n = 274, 12.5%	Lower	Slower

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Figure 2. Child BMI *z* score longitudinal growth trajectories.

Table I. Summary of biomarker measurements (number, specimen, and technique) at the 4-year visit by INMA region

	Regions			
Measurements	**Sabadell**	**Valencia**	**Asturias**	**Gipuzkoa**
HDL	n = 313 Plasma ABX-Pentra 400	n = 170 Serum ABX-Pentra 400	n = 247 Serum ABX-Pentra 400	n = 209 Serum ABX-Pentra 400
TG	n = 313 Plasma ABX-Pentra 400	n = 171 Serum ABX-Pentra 400	n = 247 Serum ABX-Pentra 400	n = 209 Serum ABX-Pentra 400
Leptin	n = 250 Plasma Multiplex			n = 209 Plasma ELISA
C-peptide	n = 250 Plasma Multiplex			n = 209 Serum ELISA
Adiponectin	n = 75 Plasma Multiplex			
Apo A1	n = 313 Plasma ABX-Pentra 400			n = 209 Serum standard
Apo B	n = 313 Plasma ABX-Pentra 400			n = 209 Serum standard
IL-6	n = 33 Plasma Multiplex			n = 209 Serum ELISA
CRP	n = 269 Plasma Abx-Pentra 401	n = 154 Serum Turbidimetry	n = 53 Serum Turbidimetry	n = 209 Serum Turbidimetry

ELISA, enzyme-linked immunosorbent assay.

Table II. Summary of biomarker measurements at the 4-year visit by INMA region

	Regions			
Measurements	**Sabadell**	**Valencia**	**Asturias**	**Gipuzkoa**
HDL, mg/dL	n = 313 51.81 (9.99)	n = 170 58.64 (11.96)	n = 247 56.49 (13.33)	n = 209 45.13 (11.51)
TG, mg/dL	n = 313 81.89 (40.22)	n = 171 54.01 (18.86)	n = 247 80.74 (44.16)	n = 209 87.95 (38.87)
Leptin, ng/mL	n = 250 2286.32 (2281.89)			n = 209 3.72 (4.07)
C-peptide, ng/mL	n = 250 2.12 (1.79)			n = 209 1.66 (0.84)
Adiponectin, ng/mL	n = 75 27 355.49 (11 801.88)			
Apo A1, ng/mL	n = 313 154.10 (30.80)			n = 209 144.49 (20.18)
Apo B, ng/mL	n = 313 75.71 (14.14)			n = 209 81.25 (17.38)
IL-6, ng/mL	n = 33 92.81 (113.38)			n = 209 2.75 (1.85)
CRP, mg/dL	n = 269 0.25 (0.66)	n = 154 0.26 (0.65)	n = 53 0.24 (0.52)	n = 209 0.29 (0.74)

Biomarker data are presented as mean (SD). The analyses used age-, sex-, and region-specific *z* scores for these biomarkers.

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Table IV. Characteristics of mothers and children by child longitudinal BMI trajectories in the INMA project (n = 2195)

Characteristics	Class 1 (n = 263; 12.0%)	Class 2 (n = 574; 26.2%)	Class 3 (n = 293; 13.4%)	Class 4 (n = 791; 36.0%)	Class 5 (n = 274; 12.5%)	*P* value
Maternal characteristics						
Age at delivery, y, mean (SD)	30.5 (4.1)	30.8 (4.3)	31.0 (3.9)	30.8 (4.2)	31.0 (4.2)	.721
Smoking in pregnancy, %						
No	80.2	83.1	79.4	82.8	86.5	.191
Yes	19.9	16.9	20.6	17.2	13.5	
Social class, %						
I + II	19.0	21.6	27.3	22.9	21.9	.350
III	27.0	27.4	22.9	28.2	24.8	
IV + V	54.0	51.0	49.8	48.9	53.3	
Education level, %						
Primary or less	25.1	23.3	20.3	23.0	21.9	.650
Secondary	41.4	42.7	39.2	40.9	44.5	
University	33.5	34.0	40.5	36.1	33.6	
Physical activity, METS (h/d), mean (SD)	37.2 (3.2)	37.5 (3.0)	37.6 (2.9)	37.2 (3.1)	37.3 (3.2)	.163
Prepregnancy BMI, kg/m^2, mean (SD)	24.4 (4.4)	23.7 (4.2)	24.2 (4.5)	23.3 (4.3)	22.6 (3.6)	<.001
Third trimester EI, kcal/d, mean (SD)	2061.2 (536.6)	2067.0 (528.2)	2020.5 (507.8)	2048.8 (534.2)	2100.9 (529.2)	.449
rMED third trimester, mean (SD)	7.8 (2.4)	8.1 (2.6)	8.1 (2.5)	8.0 (2.7)	7.8 (2.7)	.298
Gestational weight gain, kg/wk, mean (SD)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	<.001
Parity, %						
Primiparous	53.4	49.3	67.6	56.3	67.0	<.001
Multiparous	46.6	50.7	32.4	43.7	33.0	
Child characteristics						
Sex, %						
Female	41.4	47.7	48.1	52.7	43.1	.007
Male	58.6	52.3	51.9	47.3	56.9	
Age at measurement, y, mean (SD)	4.4 (0.2)	4.4 (0.2)	4.4 (0.2)	4.4 (0.2)	4.4 (0.2)	.559
INMA region, %						
Asturias	22.1	16.4	27.7	16.8	13.9	<.001
Gipuzkoa	24.7	25.4	25.6	24.5	20.8	
Sabadell	24.3	25.3	21.8	25.8	29.5	
Valencia	28.9	32.9	24.9	32.9	35.8	
Gestational age, wk, mean (SD)	39.7 (1.3)	39.8 (1.2)	39.4 (1.5)	39.7 (1.5)	39.4 (1.9)	<.001
Birth weight, kg, mean (SD)	3556.4 (397.6)	3485.4 (373.9)	3250.5 (348.6)	3296.7 (363.1)	3070.0 (375.0)	<.001
BMI *z* score at 4 y, mean (SD)	1.8 (1.0)	0.7 (0.7)	1.3 (1.0)	0.3 (0.8)	−0.5 (0.8)	<.001
WC *z* score at 4 y, mean (SD)	0.9 (1.1)	0.0 (0.8)	0.6 (1.1)	−0.2 (0.8)	−0.7 (0.7)	<.001
Metabolic risk score at 4 y, mean (SD)	1.2 (1.3)	−0.1 (1.5)	0.4 (1.7)	−0.4 (1.4)	−0.9 (1.1)	<.001
SBP *z* score at 4 y, mean (SD)	0.3 (1.0)	0.0 (1.0)	−0.1 (0.8)	−0.1 (1.0)	0.0 (1.1)	.004
DBP *z* score at 4 y, mean (SD)	0.2 (1.0)	0.0 (1.0)	−0.1 (0.8)	0.0 (1.0)	0.0 (1.1)	.024
HDL *z* score at 4 y, mean (SD)	−0.1 (0.9)	0.1 (1.1)	−0.1 (1.0)	0.0 (1.0)	0.1 (0.9)	.129
TG *z* score at 4 y, mean (SD)	0.1 (1.0)	0.0 (1.0)	0.0 (0.9)	0.0 (1.1)	−0.2 (0.8)	.268
Leptin *z* score at 4 y, mean (SD)	0.7 (1.7)	−0.1 (0.6)	0.4 (1.3)	−0.2 (0.8)	−0.3 (0.4)	<.001
C-peptide *z* score at 4 y, mean (SD)	0.3 (1.3)	0.0 (1.0)	0.2 (1.0)	−0.1 (0.9)	−0.3 (1.0)	.009
Adiponectin *z* score at 4 y, mean (SD)	0.2 (1.1)	−0.2 (0.9)	0.1 (1.1)	−0.2 (1.0)	0.4 (0.9)	.530
Apo A1 *z* score at 4 y, mean (SD)	0.0 (1.0)	0.1 (1.1)	−0.3 (0.9)	0.0 (1.0)	0.0 (0.9)	.174
Apo B *z* score at 4 y, mean (SD)	0.1 (0.8)	0.1 (1.0)	−0.1 (1.1)	0.0 (1.0)	−0.3 (0.9)	.035
IL-6 *z* score at 4 y, mean (SD)	0.3 (1.5)	−0.1 (1.0)	0.1 (0.9)	−0.1 (0.9)	−0.1 (0.7)	.290
CRP *z* score at 4 y, mean (SD)	−0.1 (0.8)	−0.1 (0.8)	0.2 (1.3)	0.0 (1.0)	0.1 (1.0)	.292

EI, energy intake; *METS*, metabolic equivalents.

Table VII. Associations of maternal adherence to the Mediterranean diet at the first trimester of pregnancy and offspring growth trajectories from birth to age 4 years in the INMA project (n = 2233)

	Model 1					Model 2				
rMED, range	2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9), RR (95% CI)	High: T3 (10-15), RR (95% CI)	*P* for trend	2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9), RR (95% CI)	High: T3 (10-15), RR (95% CI)	*P* for trend
Class 1 (n = 267): larger birth size, accelerated growth	0.96 (0.86-1.08)	Ref	0.89 (0.63-1.26)	0.99 (0.70-1.39)	.884	1.00 (0.89-1.12)	Ref	0.93 (0.66-1.33)	1.09 (0.77-1.56)	.669
Class 2 (n = 581): larger birth size, slower growth	1.02 (0.93-1.11)	Ref	1.27 (0.97-1.64)	1.19 (0.91-1.56)	.158	1.03 (0.94-1.12)	Ref	1.29 (0.99-1.69)	1.24 (0.94-1.63)	.107
Class 3 (n = 299): smaller birth size, accelerated growth	1.00 (0.90-1.12)	Ref	1.05 (0.76-1.46)	1.00 (0.72-1.40)	.956	0.99 (0.89-1.11)	Ref	1.02 (0.73-1.42)	0.95 (0.67-1.34)	.781
Class 5 (n = 284): smaller birth size, slower growth	0.98 (0.88-1.09)	Ref	1.30 (0.94-1.81)	1.13 (0.80-1.60)	.391	0.93 (0.83-1.05)	Ref	1.24 (0.89-1.73)	1.01 (0.71-1.44)	.854

rMED score ranged from 0 to 15 in 3 tertiles representing low (T1), medium (T2), and high (T3) adherence to the Mediterranean diet. The reference group for the outcome is class 4 (average birth size, slower growth trajectory); n = 802.
Model 1: Multinomial logistic regressions adjusted for child sex, age, and region.
Model 2: Model 1 further adjusted for maternal age, maternal prepregnancy BMI, smoking during pregnancy, maternal total EI, gestational weight gain, physical activity (first trimester), and parity.

Table VIII. Associations of maternal adherence to the Mediterranean diet at the first trimester of pregnancy and offspring cardiometabolic risk score, components of the score, and related biomarkers at age 4 years

	Model 1					Model 2				
rMED range	2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9), β (95% CI)	High: T3 (10-15), β (95% CI)	*P* for trend	2-unit increase	Low: T1 (1-7)	Medium: T2 (8-9), β (95% CI)	High: T3 (10-15), β (95% CI)	*P* for trend
Metabolic risk score* (n = 707)	0.01 (–0.09 to 0.10)	Ref	–0.01 (–0.28 to 0.26)	–0.02 (–0.31 to 0.27)	.873	0.01 (–0.08 to 0.11)	Ref	0.00 (–0.27 to 0.27)	0.02 (–0.27 to 0.51)	.905
WC z score* (n = 1441)	–0.01 (–0.06 to 0.03)	Ref	–0.05 (–0.17 to 0.08)	–0.08 (–0.21 to 0.05)	.206	–0.01 (–0.03 to 0.02)	Ref	0.02 (–0.06 to 0.09)	0.00 (–0.09 to 0.08)	.972
SBP z score† (n = 1385)	0.01 (–0.04 to 0.05)	Ref	–0.07 (–0.19 to 0.06)	0.01 (–0.13 to 0.14)	.934	0.01 (–0.03 to 0.06)	Ref	–0.05 (–0.18 to 0.07)	0.03 (–0.11 to 0.17)	.811
DBP z score† (n = 1385)	0.00 (–0.04 to 0.04)	Ref	–0.15 (–0.27 to –0.02)	–0.03 (–0.16 to 0.11)	.421	0.01 (–0.04 to 0.05)	Ref	–0.13 (–0.26 to –0.01)	–0.01 (–0.15 to 0.13)	.619
HDL z score‡ (n = 950)	0.00 (–0.05 to 0.05)	Ref	0.07 (–0.08 to 0.22)	–0.03 (–0.18 to 0.13)	.829	–0.01 (–0.06 to 0.05)	Ref	0.06 (–0.10 to 0.21)	–0.04 (–0.20 to 0.12)	.676
TG z score‡ (n = 951)	0.03 (–0.02 to 0.08)	Ref	0.15 (–0.01 to 0.30)	0.04 (–0.12 to 0.20)	.492	0.03 (–0.02 to 0.08)	Ref	0.15 (–0.01 to 0.30)	0.04 (–0.12 to 0.21)	.496
Leptin z score§ (n = 460)	0.02 (–0.05 to 0.10)	Ref	0.19 (–0.04 to 0.42)	0.01 (–0.22 to 0.23)	.895	–0.01 (–0.07 to 0.06)	Ref	0.14 (–0.05 to 0.34)	–0.05 (–0.24 to 0.14)	.646
C-peptide z score§ (n = 460)	–0.02 (–0.10 to 0.05)	Ref	0.09 (–0.14 to 0.32)	–0.11 (–0.33 to 0.12)	.377	–0.04 (–0.11 to 0.03)	Ref	0.05 (–0.18 to 0.28)	–0.15 (–0.38 to 0.08)	.202
z Adiponectin§ (n = 75)	–0.14 (–0.34 to 0.05)	Ref	–0.20 (–0.72 to 0.31)	–0.51 (–1.22 to 0.19)	.139	–0.12 (–0.35 to 0.11)	Ref	–0.16 (–0.74 to 0.43)	–0.46 (–1.21 to 0.29)	.228
z Apo A1¶ (n = 524)	0.09 (0.02 to 0.16)	Ref	0.07 (–0.14 to 0.28)	0.26 (0.05 to 0.46)	.017	0.10 (0.03 to 0.17)	Ref	0.08 (–0.13 to 0.26)	0.28 (0.07 to 0.49)	.011
z Apo B¶ (n = 524)	0.05 (–0.02 to 0.12)	Ref	–0.02 (–0.24 to 0.19)	–0.03 (–0.24 to 0.18)	.781	0.04 (–0.03 to 0.11)	Ref	–0.05 (–0.26 to 0.17)	–0.06 (–0.27 to 0.16)	.596
z IL-6** (n = 243)	0.03 (–0.07 to 0.13)	Ref	0.19 (–0.14 to 0.52)	0.15 (–0.17 to 0.47)	.377	0.03 (–0.07 to 0.14)	Ref	0.20 (–0.13 to 0.53)	0.15 (–0.18 to 0.48)	.387
z CRP** (n = 684)	–0.05 (–0.11 to 0.01)	Ref	–0.02 (–0.20 to 0.17)	–0.08 (–0.27 to 0.11)	.405	–0.04 (–0.11 to 0.02)	Ref	–0.01 (–0.20 to 0.18)	–0.06 (–0.26 to 0.13)	.525

rMED score ranges from 0 to 15, in 3 tertiles representing low (T1), medium (T2), and high (T3) adherence to the Mediterranean diet. Metabolic risk score: sex-, age-, and region-specific HDL *z* score, TG *z* score, average between height, age-, sex-, and region-specific SBP and DBP *z* scores and sex-, age-, and region-specific WC *z* score. Based on IDEFICS score.

Model 1: General linear regressions adjusted for child sex, age, and region.

*Model 2: General linear regressions adjusted for child sex, age, region, maternal educational level, maternal total EI, parity, and child BMI *z* score at 4 years.

†Model 2: General linear regressions adjusted for child sex, age, region, maternal educational level, maternal total EI, maternal prepregnancy BMI, gestational weight gain, and maternal physical activity.

‡Model 2: General linear regressions adjusted for child sex, age, region, maternal social class, maternal total EI, maternal prepregnancy BMI, gestational weight gain, and maternal physical activity.

§Model 2: General linear regressions adjusted for child sex, age, region, maternal educational level, maternal smoking, maternal total EI, maternal prepregnancy BMI, gestational weight gain, parity, and child BMI *z* score at 4 years.

¶Model 2: General linear regressions adjusted for child sex, age, region, maternal age, maternal smoking, maternal prepregnancy BMI, gestational diabetes, maternal total EI, and parity.

**Model 2: General linear regressions adjusted for child sex, age, region, maternal age, maternal educational level, maternal smoking, maternal total EI, and maternal physical activity.